A PECULIAR INTRALOBULAR CIRRHOSIS OF THE LIVER PRODUCED BY THE PROTOZOAL PARASITE OF KALA-AZAR

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In my report on Kala-azar, published in 1897, I described a dropsical form of the disease, which appeared, in part at least, to be produced by cirrhosis of the liver, which was found in one case post mortem. More recent experience has shown this complication to be commoner in the more chronic sporadic form of kala-azar, which is so frequent in Calcutta, than it was in the Assam epidemic disease. These cases, however, were very difficult to verify by finding the parasite by spleen puncture on account of the organ receding into the abdominal fluid before the point of the needle, although the characteristic history, greatly enlarged spleen and leucopenia, left no doubt in the mind of an experienced physician regarding the true nature of the cases. Some degree of fibrosis of the liver was described in my first 1897 report, while about a year ago a post mortem on a chronic case of kala-azar, which died with all the classical symptoms of cirrhosis of the liver, has enabled me to study the advanced stages of the affection. I, therefore, propose in the present paper to give a somewhat fuller account of the affection than the note in my work on Fevers in the Tropics, in which the photograph of a kala-azar patient suffering from this type of cirrhosis of the liver is given (opposite page 67). The following are the notes of the case referred to above.

CHRONIC SPORADIC KALA-AZAR TERMINATING WITH CIRRHOSIS OF THE LIVER

The patient was a Hindu male, aged about 30. He had suffered from enlarged spleen with frequent attacks of fever on and off for five or six years. During the last six months he had taken country liquor, but not in excess. He was in hospital for 35 days before his death, during which time he suffered from ascites with enlargement of the liver and spleen, and persistent diarrhoea, and was greatly emaciated and anaemic, and had a troublesome cough. No malarial parasites could be found in his blood, and he only occasionally had a slight rise of temperature. The disease was diagnosed as kala-azar.

A post mortem was performed and the following conditions noted. The body was extremely emaciated, and the subcutaneous fat was very scanty. The peritoneal cavity contained 30 ozs. of clear fluid, but there was no oedema of the legs, the dropsy having decreased with the diarrhoea while in hospital. The pleural cavities showed some fibrous adhesions, but the lungs were crepitant throughout, although slightly congested at the bases. Both the parietal and visceral pericardium showed extensive haemorrhages (these being common in kala-azar in various positions). The heart muscle was somewhat pale, but firm. The stomach showed petechial haemorrhages in the mucous membrane. The small intestines showed a few points of haemorrhage due to the bites of a small number of anchylostomata (such as are found in 75 per cent. of post mortems in natives in Calcutta), but were quite free from ulceration. The large intestine showed some pigmented scars, while the mucous membrane of the lower part was congested and oedematous. The liver weighed 29 ozs. (the body weight was only 60 lbs.). The surface was perfectly smooth, and of a greenish brown colour. It cut very firmly, and its substance could not be broken down by very firm digital pressure. The gall bladder was healthy. The spleen weighed 12½ ozs., having become much diminished in size during the continuance of the diarrhoea. The capsule was wrinkled, and on section it was a brownish-red colour and very firm, owing to excess of fibrous tissue. The kidneys were healthy except that the capsule stripped with some difficulty, but left a smooth surface. The brain was healthy.

MICROSCOPICAL EXAMINATION

The protozoal parasites of kala-azar were found in large numbers in the bone marrow, spleen and liver, being mostly of the small size seen in chronic cases of the disease. In the liver they were found with an oil immersion lens in the endothelial cells of the capillaries between the columns of hepatic cells in specially prepared specimens. With haematoxylin and eosin only very fine dots could be detected in this position, being the nuclei of the parasites, closely resembling pigmentation, for which I think I must have sometimes mistaken them in my original Assam investigation in 1896. The persistence of the parasites in the advanced cirrhotic stage of the organ is remarkable, and leaves little doubt that they are the cause of this peculiar intralobular cirrhosis.

The general appearance of the liver under a low magnification (Zeiss A. Oc. 2) is shown in fig. 1 of Plate I. To the left is seen a portion of the capsule at the site of an extensive fibrous band, but it will be observed that there is no marked depression of the surface such as produces the hobnail appearance of the common atrophic cirrhosis of the liver. The capsule itself also shows but very slight thickening. The most striking feature is the universal distribution of the cirrhotic process throughout the liver lobules, so that the hyperplastic connective tissue widely separates each column of epithelial liver cells, and, indeed, makes up the greater bulk of the lobules from the portal to the hepatic venules. A careful study of a number of sections showed that there is extremely little alteration in the general arrangement of the liver lobules, which retain to a great extent their shape and size, although the intralobular veins are somewhat less prominent than usual. There is distinct cellular and fibrous increase around the portal interlobular veins, but not extending far round the circumference of the liver lobules as a rule, so that the organ is not cut up into small areas of hepatic substance by complete circles of fibrous tissue, as in atrophic cirrhosis. This explains the absence of the typical yellow lobulated appearance to the naked eye on section of the organ, which is so characteristic of hobnail liver, and has probably led to the new form having been frequently overlooked, especially in its less marked degrees. The perilobular portal tissue shows a few well-marked bile-duct-like double columns of some-

what cubical epithelial cells, but these are nothing like so numerous as in hypertrophic cirrhosis of the liver, being, indeed, scarcely more evident than in the atrophic form.

Fig. 2 of Plate I shows a portion of a liver lobule under a higher magnification (Zeiss A, Oc. 2), and includes some of a periportal fibrous band. The very great increase of the intercellular connective tissue of the lobule will be at once apparent, the epithelial cells forming barely half of the area of the lobule, each column of liver cells being separated from the next by an extensive layer of fibro-cellular connective tissue. In places the liver cells contained much yellow pigment derived from broken down red cells anaemia being a marked symptom of the later stages of kala-azar, although frequently only slight in degree in the first few months of the disease, much less so than in true malarial fever of any duration. With this exception the surviving liver cells have a fairly healthy appearance, and stain well. The connective tissue between the liver cells is partly fibrous, but chiefly consists of small round cells together with a considerable number of larger epitheloid-like ones, some of considerable size. It is the latter which were found to still contain the parasites of kala-azar in specially stained sections, and they are doubtless the enlarged endothelial cells of the capillary vessels, which S. R. Christophers first described as containing the human stage of the kala-azar parasite.

This distribution of the organism at once furnishes the key to the peculiar position of the connective tissue proliferation. These minute protozoa multiply in the endothelial cells, and on reaching their full size some of the cells rupture, scattering the parasites into the blood stream, where they are found in comparatively small numbers, in the polynuclear leucocytes more particularly. These bring them back again to the liver, spleen and bone marrow, where the cycle is repeated. When this process continues for a number of years, as in the chronic form in which alone I have seen cirrhosis of the liver supervene, it is not surprising that eventually the constant irritation of the parasite causes proliferation of the connective tissue around the capillary vessels throughout the liver lobules, and to a less extent in Glisson's capsule, around the portal radicles, and so produces the condition above described. This universal thickening round the capillary vessels of the liver causes both an extensive

atrophy of the hepatic cells and also must considerably retard the circulation of the portal blood. It thus produces the marked ascites, which, although the fluid accumulates much less rapidly than in atrophic cirrhosis, yet is a formidable and not infrequently fatal complication in these unfortunate people, worn out as they are by years of fever, and reduced to an extremely debilitated and emaciated state.

FREQUENCY OF INTRALOBULAR CIRRHOSIS OF THE LIVER IN KALA-AZAR

Among 48 post mortems I have performed on sporadic kala-azar in Calcutta in the last few years, marked cirrhotic changes were present in the liver in four; while in seven more, slighter degrees of fibrosis were met with. The latter number is certainly too low, for in half the cases the exact consistence of the organ was not recorded in the post mortem notes, and this degree is very easily overlooked. On the other hand, the liver was noted to be softer than normal in nine cases, so even slight fibrosis is very far from being constantly met with. This is due to the extreme variation in the duration of this fever, namely, from a few months to five to ten years. In my work on Fevers in the Tropics a table of the degree of enlargement of the liver in different stages of kala-azar is given, from which it appears that marked enlargement of the liver is rarely seen before the end of six months fever, while the cirrhotic condition usually only appears after several years illness.

MALARIAL CIRRHOSIS OF THE LIVER

In view of the fact that until the last few years kala-azar has always been classed as 'malarial cachexia,' the discovery of the above-described form of cirrhosis due to kala-azar raises the question as to how far descriptions of malarial cirrhosis of the liver may have been based on cases of kala-azar erroneously diagnosed as malarial. In this connection it is worth recording that in five years pathological experience at the Medical College, Calcutta, I have only once met with a case of undoubted malarial cirrhosis of the liver, in which the microscopical picture of uniform extensive thickening of the perilobular connective tissue with much black pigment in its lymph spaces, and to a less extent in the intracellular tissue throughout the

liver lobules, was so characteristic that it could not possibly be overlooked. My impression, therefore, is that a true malarial cirrhosis of the liver does occur, but that it is certainly decidedly rare even in highly malarious Lower Bengal, for a large proportion of our cases come from the unhealthy districts surrounding Calcutta.

I may also mention that typical atrophic cirrhosis is extremely common in Bengal, more so even than in Europe, although it is certainly not as a rule due to alcohol. Major O. W. Sutherland has also recorded a similar experience in the Punjab. Thus in five per cent. of over 4,000 post mortems in Calcutta cirrhosis of the liver was found, although 40 per cent. of the deaths were from typically tropical diseases, such as cholera, &c. If these are excluded the percentage rises to between 8 and 9 per cent. of the deaths. On the other hand, in Berlin Forster found cirrhosis of the liver in but 1 per cent. of 3,200 post mortems. This very important subject, however, is beyond the scope of the present paper.

SUMMARY

1. The most chronic cases of kala-azar not infrequently terminate their course with ascites due to cirrhosis of the liver.

2. The cirrhosis is of a peculiar intralobular type of uniform distribution and with a smooth surface to the organ.

3. It is due to the protozoal parasite of kala-azar, which may be found in the liver and other organs after death.

4. This form of cirrhosis of the liver is much commoner in Lower Bengal than a true malarial cirrhosis, with which it has probably hitherto been confused. It is, however, much less common than atrophic cirrhosis due to unknown causes.